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Maternal microchimerism

Friend or foe in type 1 diabetes?

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Increased levels of non-inherited maternal HLA alleles have been detected in the periphery of children with type 1 diabetes and an increased frequency of maternal cells has been identified in type 1 diabetes pancreas. It is now clear that the phenotype of these cells is pancreatic,[1] supporting the hypothesis that maternal cells in human pancreas are derived from multipotent maternal progenitors. Here we hypothesize how increased levels of maternal cells could play a role in islet autoimmunity.

Type 1 diabetes (T1D) results from the autoimmune destruction of insulin producing β cells in the pancreas. The condition is mutlifactorial with twin studies indicating an etiology that is approximately 50% genetic and 50% environmental.[2] Stochastic events such as epigenetic changes or lymphocyte repertoire may play a role in determining T1D development.[3] Environmental components modulate genetic risk but their identities have remained elusive. Viral infections,[4] early feeding,[5-7] gut microbiota,[8] and maternal influences[9] have all been postulated to play a role but none unequivocally proven.

The appearance of islet autoantibodies,[10] precise markers of future T1D rarely occurs in infants before 6 months and rapidly reaches peak incidence around the age of two years in children at high genetic risk.[11] This accumulating evidence suggests that the pre- and perinatal periods are important in the development of T1D.

Maternal microchimerism (MMc) is acquired by an infant during pregnancy and these maternal cells are maintained in some individuals for decades.[12] Maternal cells can protect themselves from detection by the developing fetal immune response by inducing fetal T cell progenitors to differentiate into functionally suppressive regulatory T cells.[13] Nevertheless, encountering maternal antigens during pregnancy represents the first immunological challenge for the fetus and could influence tolerance to antigens encountered in utero.

MMc Exist in Multiple Pancreatic Cell Subsets

Insulin positive MMc were detected in human pancreases in previous studies.[14,15] To further evaluate the phenotype of MMc, markers for different pancreatic cell lineages were analyzed and maternal cells were identified in nine normal male autopsy pancreases investigated (age range from gestational to adolescence) with cells positive for pancreatic endocrine, exocrine, and ductal markers. Within the endocrine compartment, MMc were enriched in the β cell fractions with frequencies between 0.38–1.4% and were rare in other islet cell types. Since endocrine and exocrine cells are derived from common progenitors, these findings indirectly suggest that some maternal cells transferred in pregnancy are pancreatic progenitors supporting previous studies in humans and mice.[16-18]

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Maternal T Cells Do Not Infiltrate Islets of Host Pancreas

A pilot study in 2007[15] detected significantly higher levels of MMc in peripheral blood DNA from patients with T1D than age-matched controls. Maternal cells have been proposed to (1) be targets of host immune responses; (2) facilitate immune attack; or (3) repair tissue damage in response to injury.

The overall aims of our studies have been to determine whether maternal microchimerism could contribute to risk of T1D. Previous studies in our laboratory showed that the frequency of female cells in T1D pancreas was increased.[14] More recent examination of eight male pancreases with recent-onset or long-standing T1D, using concomitant X/Y chromosome FISH and immunofluorescence revealed no female CD45+ cells in the insulitic infiltrate in T1D islets indicating that maternal cells do not directly kill host islet β cells.

The Frequency of MMc β Cells is Increased in T1D Pancreas but MMc Are Not Replicating in Response to Islet Injury

In pancreases of both recent-onset and long-standing T1D patients, the levels of total MMc as well as MMc β cells were significantly higher than age-matched controls (0.68 ± 0.07% vs. 0.39 ± 0.09% [P = 0.03] and 2.34 ± 0.5% vs. 0.66 ± 0.2% [P = 0.01], respectively). Replication in T1D islets has been reported previously.[19] We therefore hypothesized that the increased MMc frequency observed may be due to replication of maternal β cells. Our study showed that the replicating cells in islets were not CD45+ in origin and subsequently that these replicating cells in male pancreas with ongoing insulitis were not derived from female cells. The reason why MMc frequency is increased in T1D β cells remains unclear. Some suggest that chimeric β cells may be resistant to autoimmune destruction. Another possibility is that an increased frequency of islet β cells of maternal origin may contribute to the initiation of autoimmunity.[20]

Can Allo-Immunity Be Shifted to Autoimmunity in Type 1 Diabetes?

An intriguing hypothesis is that elevated levels of MMc β cells in pancreas or peripheral blood cells might initiate an allo-immune response. It is possible that in situations where NIMA specific tolerance is lost or altered in postnatal immune development, MMc β cells above a certain frequency threshold could become targeted by the "host" immune system. This initial allo-immune response may shift the immune balance toward autoimmunity via molecular mimicry as previously described in chronic rejection.[21] It is well established that the neonatal pancreas undergoes extensive morphological remodelling with β cell proliferation[22] accompanied by a transient wave of apoptosis.[23,24] The accumulation of apoptotic β cells with defective clearance could lead to cell necrosis thus activating the immune system. Perhaps maternal islet autoantigens released by dying β cells could initiate an immune response which is later shifted to autoimmunity, as demonstrated in a murine model of microchimerism by Roy E et al.[25] Alternatively, islet autoantigens presented on maternal antigen presenting cells (APCs) could prime host T cells. A recent study suggested that the antigen presenting capacity of cord blood naïve monocytes was reduced due to low expression of molecules involved in presentation and co-stimulation but normalized after 8 months of age when islet autoimmunity appears.[26] This observation suggests that maternal APCs may modify the risk of activating autoreactive T cells. Neonatal development and the effect of maternal/fetal interactions is an emerging area of biology where detailed studies are required.

Can MMc Act in an Attempt to Restore Tolerance in T1D?

In the pancreases from T1D patients, there is an overexpression of genes involved in regeneration and immunoregulation, suggesting attempted amelioration of the autoimmune response and restoration the β cell mass.[27] The possibility remains that the increased frequency of MMc observed in T1D islets plays a role in immunoregulation and/or tissue repair as described in fetal microchimerism.[28] The benefits vs. risks associated with increased maternal microchimerism frequency remains unclear and accurate answers will require rigorous methodologies to study microchimerism.

Efforts to Improve Strategies to Identify Maternal Cells in Humans

In mouse models it is possible to study bi-directional transfer of cells in pregnancy using fluorescent tags. In humans the available strategies are less sophisticated. A technical limitation of labeling MMc using sex-chromosome in situ hybridization in histological samples could result in false positive counting of MMc originating from two over-lapping male host cells or a partial signal derived from a polyploid nucleus. Confocal imaging was used to help overcome this concern. As an additional confirmation, we are currently developing strategies to analyze maternal cells using combined laser capture and STR profiling as well as immunofluorescence against non-inherited maternal HLA alleles (NIMA). This however is only possible when maternal DNA is available.

Conclusion

MMc of multiple human pancreatic cell subsets were detected with enrichment in the β cell fraction. We propose that a combination of altered tolerance and increased levels of MMc in pancreatic β cells could play a role in the initiation of islet autoimmunity.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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